Takei and Ohno Laboratories (Special Issue on the Commemoration of the Fortieth Anniversary)

TAKEI LABORATORY (April 1937～October 1959)

Head: Dr. Sankichi Takei

and

OHNO LABORATORY (July 1957～)

Head: Dr. Minoru Ohno

The laboratory for chemical research of plant product was established at the Institute in 1957 and Dr. Ohno has since been in charge of directing organic chemical studies in this field.

Historically, this laboratory originated in the former Takei Laboratory and the earlier studies on organic insecticides of both plant and synthetic origins, such as pyrethrum flowers, synergists and DDT analogs, have been succeeded and developed by the present laboratory staffs. During the last decade, fifteen research associates, fourteen graduate students and two operators have joined the laboratory and contributed very much to the activities; nine Ph. D. and eight M.S. degrees have been awarded on the works performed in this laboratory. Experimental facilities and equipments involve modern instruments such as concentric-type fractionation column, gas chromatographs for qualitative and preparative purposes, auto-recording spectropolarimeter and auto-recording UV-spectrophotometer.

Inouye and Sugita have studied pyrethrum chemistry, in particular synthesis and stereochemistry of pyrethroids. They achieved for the first time the total synthesis of the naturally occurring chrysanthemumdicarboxylic acid and its geometrical isomers, thereby unequivocally establishing the hitherto unknown geometry of the side chain double bond as *trans*. The method of configurational assignment employed here is applicable to determination of geometry of double bond in general. Later on, they also discovered another novel synthetic route to chrysanthemumdicarboxylic acid from *o*-cresol, which was applied for U.S. Patent and is capable of meeting practical production of this acid.

The absolute configuration of the cyclopropane ring carbons-1 and 3 of the naturally occurring (+)-*trans, trans*-chrysanthemumdicarboxylic acid was assigned the (1R:3R)-configuration by a chemical correlation of this acid to the known (−)-(R:R)-*trans*-caronic acid. Then, the sole pending problem in stereochemistry of pyrethroids in earlier nineteen fifties was the assignment of absolute configuration of the carbon-4 of the naturally derived (+)-cinerolone and (+)-pyrethrolone, both the alcoholic moieties of cinerins, pyrethrins I and II. This was also established as (S) unambiguously by the direct chemical transformation of these dextrorotatory alcohols through degradation intermediates into (−)-methoxysuccinic acid of the well-defined (S)-configuration. The stereochemical knowledge fully supplied by the above

studies, together with the biological activity data obtained by bioassay of respective stereomeric pyrethroids, thus enabled one to discuss the relationship between the actual conformation and toxicity of pyrethroids (1957–1960:18 papers and 1 patent).

Allrethronyl esters of homologous chrysanthemic acids have been synthesized by Katsuda and esters of cyclopropane acids containing methylenedioxyphenyl grouping have been prepared by Takei in search for more effective pyrethroid type insecticides and the bioassay showed some of these esters to be effective in knock-down of housefly (1958–1960:9 papers and 1 patent).

In connection with pyrethrum, studies in search for pyrethrum synergists were made and, among many compounds synthesized, 3,4-methylenedioxyphenyl-tetrahydrofurfurylether was found to be an effective synergist (1960:2 papers and 1 patent).

The above series of studies of pyrethroid chemistry in particular of chrysanthemum acids brought about many informations of both biological and stereochemical importance and drove the group of workers to extend their study of cyclopropane chemistry to asymmetric synthesis of the system. The interest of this group concerned the study of the addition of nucleophilic and electrophilic reagents to ethylenic linkages which have an asymmetric center adjacent or near the reaction sites, to determine whether or not asymmetric synthesis will be achieved and also to reveal the steric course thereof. The addition of diazo-compounds to substituted acrylic esters resulted in partial asymmetric synthesis of cyclopropane acids and it was concluded that the Cram-Prelog model was applicable to this system. As an application of this generalization, the asymmetric synthesis of *cis*-umbellularic acid enabled one to establish the stereochemistry of all the terpenes of thujane series.

Asymmetric 3-membered ring formation in Michael type condensation, Darzens reaction and Simmons-Smith reaction has been achieved and surprising were the facts that in the former two reactions, having the similar reaction mechanism, the solvent polarity altered the steric course of these reactions and resulted in a dramatic reversal of rotation and configuration of the products and that in the latter, the Cram-Prelog model did not apply. The hitherto generally accepted concerted mechanism via a six-membered cyclic intermediate complex for the conjugate addition of Grignard reagent to α,β-unsaturated esters was revised by the successful asymmetric synthesis in this reaction exemplified by the conjugate addition of phenylmagnesium bromide to (−)-menthyl crotonate to give (+)-(S)-3-phenylbutyric acid, and it was shown that this reaction proceeded through a simple nucleophilic addition of Grignard reagent to the polarized ethylenic system of the most stable transoidal conformation, to which the Cram-Prelog model was reasonably applicable. The presence of catalytic amount of cuprous chloride, however, altered the steric course of this addition reaction and again resulted in a reversal of rotation and configuration of the products. Asymmetric synthesis in *cis*-hydroxylation with osmium tetroxide, methoxymercuration and enamine addition has also been achieved with success and has been extensively prosecuted in the hope of revealing mechanistic interpretration of these results (1960–:7 papers).

Hatanaka and his co-workers have succeeded and developed the earlier works

of leaf-alcohol and aldehyde. Leaf-alcohol and aldehyde are widely distributed in green leaves and are responsible for the characteristic green leaf odor, hence the names. They both are of biogenetic interest because they can be looked upon as constituting fragmental structure of jasmone, violet aldehyde, cucumber alcohol and other aroma of plant origin and, in addition, were found recently in some insect excretions as functioning attractant or repellent. Hatanaka isolated the *trans*-hexenol from fresh tea leaves in a minor amount together with the major *cis*-leaf alcohol and showed the *trans*-isomer thus isolated to be of natural occurrance and not an artefact during the isolation process. He also developed a novel method of preparation for leaf aldehyde in an improved yield and exploited the synthesis of all 7 isomers of leaf alcohol via intermediate hexinols. Both leaf-alcohol and aldehyde, when heated with metallic sodium or potassium, were easily aromatized to produce the same 2-propyl-5-ethylbenzylalcohol. This aromatization reaction took place uniquely with other β,γ-, and α,β-unsaturated aliphatic alcohols and aldehydes in general, and hence was designated "leaf alcohol reaction". The reaction mechanism was established as proceeding through dehydrogenation of the starting alcohols, Michael addition, aldol cyclization, dehydrogenation and aldehyde disproportionation, by means of synthesis of benzyl alcohol products via unequivocal synthetic route as well as by a stepwise model reaction with crotonaldehyde. The substituted benzyl alcohol from leaf alcohol has a lemon-like aroma characteristic of manufactured black tea and it was suspected that it might have been enzymatically produced from leaf alcohol and/or aldehyde during fermentation of tea leaves in manufacturing. An attempted search for this substance in neutral fraction of steam distillate of manufactured black tea was made, but it has not so far been detected (1957–:16 papers).

Hamada and his co-workers have been engaged in the synthesis of aromatic halogen compounds and revealed the relation between chemical structure and biological activity of the condensation products of 2,4-, and 2,5-dichlorophenol with chloral. A remarkable fungicidal rather than the expected insecticidal activity of these compounds was pointed out (1957–1960:6 papers).

Publications

(* indicates an article published in Japanese)

I. Pyrethrum Chemistry

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V. Patents

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